EDUCATIONAL COMMENTARY – PATHOGEN REDUCTION TECHNOLOGY

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Learning Objectives

On completion of this exercise, the participant should be able to
- define pathogen reduction;
- recognize the different methods for inactivating pathogens;
- explain the importance of pathogen-reduced blood products; and
- understand limitations and risks of pathogen-reduced blood products.

Introduction

Advances in donor testing over the past two decades have greatly reduced the risk for certain transfusion-transmitted infections (TTI) such as human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV, HCV, respectively), and sepsis from bacterial contamination. Unfortunately, emerging pathogens (e.g., Zika and Ebola viruses) continue to threaten the blood supply, and when no test system is available, as in the case of Chikungunya virus, blood banks rely on donor screening and selection criteria. In March 2016, the U.S. Food and Drug Administration (FDA) issued a draft guidance recommending the use of pathogen-reduction technology (PRT) or bacterial testing to further control the risk for bacterial contamination of platelets stored at room temperature. This guidance states that if PRT is used, no further bacterial testing of the platelet product will be required. Along with the FDA’s updated guidance, its recent approval of some PRT systems makes providing pathogen-reduced blood products more feasible.

Bacterial Contamination in Platelets

It is well established that platelets are associated with a higher risk for sepsis and sepsis-related fatality than any other transfusable blood component. Bacterial testing has been standard practice in blood banks since the implementation of the AABB standard in 2004 requiring a process to limit and detect bacterial contamination, and the 2014 FDA guidance for secondary platelet testing on days 4 and 5. Since then, the number of bacteria-related fatalities reported to the FDA has decreased. Yet bacterial contamination of platelets continues to be the leading cause of infections from blood transfusions, occurring in approximately 1 in 2000 to 3000 transfusions. The current process for bacterial testing requires a 24-hour hold on the platelet product before sampling for testing. With the new FDA guidance, the donor service personnel can treat the platelet product with PRT immediately, reducing the time before the product can be distributed and eliminating the need for bacterial testing. There is also potential to extend the shelf life of platelet products to 7 days. Pathogen-reduction technology can inactivate not only bacteria, but other pathogens as well, reducing the risk for TTI.
Pathogen-Reduction Technology
Pathogen-reduction technology uses chemical or biological mechanisms to inactivate pathogens in a blood product and has been used for over 20 years. Pathogen-reduction technologies can be divided into photosensitive and non-photosensitive methods.² Currently, the FDA has approved these technologies only for use with platelets and plasma. Methods of PRT to be used on red blood cells and whole blood are currently undergoing evaluation, but none is yet approved for use. The difficulty in developing PRT for red blood cells and whole blood is that the photosensitive methods require a large dose of ultraviolet light (UV), and some non-photosensitive methods destroy the cell membrane. Depending on the method, PRT may inactivate pathogens such as bacteria, viruses, and protozoan parasites, and it is especially valuable for emerging pathogens for which screening test methods are unavailable. Pathogen-reduction technology may allow for safer transfusions, significantly decrease the threat of TTI, and eliminate some donor screening procedures reducing the number of deferrals. Several PRT technologies exist, although currently only the INTERCEPT system (Cerus Corp) and Octaplas solvent/detergent method (Octapharma) are approved by the FDA for use in the United States.

Photosensitive Compounds
The following methods and techniques use photosensitive compounds to induce an excited state, causing the molecules in the target (DNA) to undergo chemical reactions.

Psoralen/UVA
The INTERCEPT system uses the psoralen amotosalen. Amotosalen was chosen because of its ability to inactivate pathogens while maintaining the integrity of the blood product. INTERCEPT was approved for use in the United States in December 2014 and is currently used for platelets and plasma products only. The amotosalen targets DNA and RNA; when activated by exposure to UV light between 320 and 400 nm (UVA), it initiates permanent cross-linking between the nucleic acids. This cross-linking blocks the replication of the target cells, rendering them inactive. Following treatment, the amotosalen is removed via filter and a compound adsorption device.⁴ An advantage to this PRT process is that, because the T lymphocytes are inactivated, these platelet products are rendered cytomegalovirus-negative, negating the need for irradiation to prevent transfusion-associated graft-vs-host disease. This process renders about 30% of the platelets inactive, but the remaining treated platelets are hemostatically functional. Platelets treated with the INTERCEPT method have been demonstrated in clinical trials to be effective against leukocytes and a broad spectrum of pathogens, although some nonenveloped viruses (HAV, HEV, parvovirus B19, and poliovirus) and bacterial spores have been shown to be resistant to this treatment.⁵ This treatment is also ineffective against prions. A Cochrane review evaluated nine randomized controlled trials and concluded that there was no evidence of a difference in mortality, bleeding, transfusion reactions, or adverse events between INTERCEPT platelets and standard (untreated) platelets.⁶ There was, however, a significantly lower platelet response in patients who received the
pathogen-reduced platelets vs. those who received standard platelets, and the patients receiving the INTERCEPT platelets required 7% more platelets than those who received the standard platelets.

There are a few theoretical risks and limitations of INTERCEPT platelets. These products are contraindicated in patients with a hypersensitivity reaction to psoralens and for neonates treated with phototherapy devices that emit a peak energy wavelength less than 425 nm. In one randomized trial involving adults, an increase in acute respiratory distress syndrome was reported among platelet transfusion recipients.4 Another trial showed an increase in cardiac events in recipients of amotosalen-treated plasma.4 Cerus is currently developing another INTERCEPT technology for use on packed red blood cells. It uses an alkylating agent, S-303 frangible anchor linker effector (FRALE), to irreversibly cross-link with DNA and RNA nucleic acids.7 When FRALE was first evaluated more than a decade ago, recipients experienced a significant increase in constipation and development of red blood cell antibodies. Cerus has since developed a second generation of this product, which is undergoing a phase III clinical trial in Europe.

Riboflavin/UV

Riboflavin (vitamin B2) is used in the Mirasol system manufactured by Terumo BCT. The blood product is mixed with the riboflavin solution and is placed in an illuminator, where it is exposed to UV light. On activation by UV light of 265 to 370 nm, the riboflavin oxidizes guanine residues in DNA and RNA, inactivating bacteria, viruses, leukocytes, and other potential bloodborne pathogens.8 Because riboflavin and its photoproducts are already present in human blood, there is no need for filtration. Although Mirasol PRT is effective in the treatment of whole blood and red blood cells, it is not licensed anywhere for this use. Like INTERCEPT, Mirasol is not effective against bacterial spores.7 The Mirasol system for plasma and platelets is not available in the United States.

Ultraviolet C Light

The THERAFLEX system, manufactured by Macopharma, uses ultraviolet C (UVC) light (254 nm) to inactivate bacteria, viruses, and protozoa in platelet products. The reactivity of UVC is quenched in more turbid solutions or solutions containing protein; therefore, THERAFLEX is only effective in platelets suspended in platelet additive solutions.5 There is little risk for toxicity because no photoactive chemical is added to the product. THERAFLEX is currently in phase III clinical trials. One possible limitation is that HIV has been shown to be resistant to UVC light.7

Methylene Blue

Macopharma also manufactures a THERAFLEX system that incorporates methylene blue, 630-nm visible light, and filtration. This system inactivates pathogens in plasma by interacting with the nucleic acids.
Because methylene blue alone is ineffective against intracellular pathogens, the plasma must be filtered before treatment.  

**Non-photosensitive Methods**

**Solvent/Detergent**

Solvent/detergent (S/D) methods were developed in the 1980s. The membrane of enveloped viruses is disrupted by the S/D, inactivating the pathogen. Oil extraction and chromatography remove the S/D from the product. Because of the mechanism, S/D techniques are ineffective against nonenveloped viruses (e.g., HAV, HEV, parvovirus B19) and cannot be used on cellular products, because they would destroy the lipid bilayer. Another limitation of this method is that plasma products treated with S/D are known to reduce coagulation factor activity. Factor VIII activity in Octaplas plasma is approximately 10% to 20% reduced compared with untreated fresh frozen plasma. The FDA approved the S/D plasma product Octaplas, manufactured by Octapharma, in January 2013 for use as a pathogen-reduced plasma product.

**Nanofiltration**

Nanofiltration, which uses 15- to 40-nm pore-sized filters, can be used in conjunction with some other PRT methods to remove prions in plasma. This is a common method used on S/D plasma.

**Cost Considerations**

With implementation of any new technology or method, there are costs associated with equipment setup, training, and quality testing. The cost of these PRT products and processes must be taken into consideration for the donor service as well as the transfusion service; however, the widespread use of PRT may potentially reduce other current expenses, such as donor-screening expenses, donor deferrals, and costs associated with treating patients with TTI. One U.S. study estimates that using pathogen-reduced platelets could decrease the cost by $141.65 per unit; of course, costs are influenced by many factors, which vary among institutions. Currently, there is no FDA-approved PRT system that can extend the life of platelets to 7 days; however, there is potential to save costs on wastage of outdated platelets if a 7-day shelf life is approved. Pathogen-reduction technology may also help reduce costs associated with emerging pathogens. When the Zika virus appeared in the United States, donor centers in the “hot zone” were given 30 days to start testing. Much cost was associated with the response to Zika, the implementation of the test as well as increased cost of blood products. Pathogen-reduction technology is a proactive approach to protecting the blood supply.

**Summary**

No single system will eliminate all pathogens in blood. Several pathogens, such as prions, some nonenveloped viruses, and bacterial spores, are resistant to some PRT systems. It is important that the
technologies used have a broad spectrum of activity to inactivate as many pathogens as possible, at the same time maintaining proper balance between the pathogen kill and product quality. Pathogen-reduction technology has been shown to be effective in inactivating many pathogens implicated in TTI, including bacteria; however, the use of pathogen-reduced blood products is not without risk. Adverse reactions, side effects, and/or loss of product functionality should be considered before implementing PRT.

**References**


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